

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicants                 | Nicholas V. Perricone, <i>et al.</i>                    |
| Application No. 10/750,390 | Filing Date: December 31, 2003                          |
| Title of Application:      | Methods for Formulating Stabilized Insulin Compositions |
| Confirmation No. 8977      | Art Unit: 1615  |
|                            |   |

**Appeal Brief Under 37 CFR §41.37**

Mail Stop Appeal Brief - Patents  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

A Final Office Action issued in the above application on 20 August 2008.

A Notice of Appeal was filed 22 December 2008 in the above application, appealing the final rejection of claims 1-6, 8, and 11-16, all of the claims pending in the application.

Appellant submits its Appeal Brief for the above-captioned application as follows.

**(i) Real Party in Interest**

The real party in interest is Transdermal Biotechnology, Inc., 639 Research Parkway, Meriden, Connecticut, 06450, the owner of the present application.

**(ii) Related Appeals and Interferences**

Applicant has a co-pending appeal of the final rejection of U.S. Patent Application Nos. 10/750,390; 11/344,206; 11/334,442; and 11/506,137 which have related subject matter.

**(iii) Status Of Claims**

Claims 1-6, 8, and 11-16 are currently pending, stand rejected and are the subject of the instant Appeal. A copy of each of these claims is submitted in the attached Appendix.

**(iv) Status Of Amendments**

There are no pending amendments to the claims.

**(v) Summary of claimed subject matter**

Claim 1 relates to a method of formulating a topical insulin composition by mixing an insulin solution with a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier to entrap the insulin and stabilize it at room temperature.

(Specification, ¶[0007] at p. 2, lines 23-26; ¶[0009] (Page 3, line 7), ¶[0013] (Page 4)).

Claim 2 further specifies forming a polyglycol mixture, using polyglycol having a molecular weight of 200 and polyglycol having a molecular weight of 400, and shaving the phosphatidylcholine into the polyglycol mixture to form a phosphatidylcholine solution; and mixing the phosphatidylcholine solution until it is clear. (Specification, ¶[0017](Page 6, lines 17-28)).

Claim 3 further specifies that the phosphatidylcholine is polyenylphosphatidylcholine-enriched phosphatidylcholine. (Specification, ¶[0012](Page 4, lines 3-24)).

Claim 4 further specifies a preferred embodiment having 45% w/w phosphatidylcholine, 50% w/w polyglycol having a molecular weight of 200, and 5% w/w polyglycol having a molecular weight of 400. (Specification, ¶[0017](Page 6, lines 17-28)).

Claim 5 further specifies that the phosphatidylcholine solution is warmed to 40°C and milling the warmed solution; and siloxylated polyether and polydimethylsiloxane are combined to form a fluid which is added to the warmed solution; and that methyl paraben is added to the solution and milled until it dissolves; and that water warmed to 40°C is added slowly to said solution; then cooled to room temperature while sweeping it. (Specification, ¶[0019](Page 7, lines 10-23); and ¶[0018](Page 7, lines 4-9)).

Claim 6 further specifies a preferred embodiment having 53.25% w/w phosphatidylcholine solution, 1.00% w/w siloxylated polyether, 1.00% w/w

polydimethylsiloxane , 0.75% w/w methyl paraben, and 44.00% w/w water.

(Specification, ¶¶[0017-0019])(Page 6, line 17-Page 7, line 23)).

Claim 8 specifies that the siloxylated polyether is dimethyl, methyl(propylpolyethylene oxide propylene oxide, acetate) siloxane. (Specification, ¶[0018] (Page 7, lines 4-9)).

Claims 11 and 12 specifies that the insulin solution is human recombinant insulin prepared in 0.01 N HCl at 50 mg/ml. (Specification, ¶[0020] (Page 7, lines 24-28)).

Claim 13 specifies that the insulin solution is mixed into the carrier at room temperature for at least one hour. (Specification, ¶[0020] (Page 7, lines 24-28)).

Claim 14 specifies that the insulin solution is mixed into the carrier to obtain an insulin composition having a concentration of 20 mg/ml. (Specification, ¶[0020] (Page 7, lines 24-28)).

Claim 15 specifies that the carrier of claim 1 is prepared by shaving phosphatidylcholine into a polyglycol to form a phosphatidylcholine solution; and mixing the phosphatidylcholine solution until it is clear. . (Specification, ¶[0017](Page 6, lines 17-28))

Claim 16 specifies that preparing the carrier further comprises warming the phosphatidylcholine solution to 40°C and milling the warmed solution; combining siloxylated polyether and polydimethylsiloxane to form a fluid; adding the fluid to the warmed solution carrier and milling until the solution is clear; adding methyl paraben to the solution and milling until the methyl paraben dissolves in said solution; and warming water to 40°C and adding the warmed water slowly to the solution; and ceasing milling

of the solution and sweeping it to cool it to room temperature. (Specification, ¶[0019](Page 7, lines 10-23); and ¶[0018](Page 7, lines 4-9)).

**(vi) Grounds of rejection to be reviewed upon appeal**

Claims 1-6, 8, and 11-16 are rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement, on the grounds that “non-liposome multilamellar crystal non-polar phosphatidycholine” is not described in the specification.

Claims 1-6, 8, and 11-16 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention, on the grounds that “non-polar carrier” is indefinite.

Claims 1-6, 8, and 11-16 stand rejected under 35 U.S.C. §103(a) as unpatentable over Amselen et al (US 5662932) or Lynch (US 2002/0153509) in view of Hansen (US 4614730) and Patel (US6294192), and with respect to claims 2-6, 8, 15 and 16, Chaiyawat (U.S. 6538061) and Brieva (U.S. 5985298).

**(vii) Argument**

The present invention is a method of formulating a stable topical insulin composition. The importance of the present invention is that it provides a method of formulating stable topical insulin compositions that were stable for at least 22 weeks at room temperature, which is 21 weeks longer than insulin standards stored at room

temperature. [Specification, ¶21]. This is a significant benefit to diabetic patients, particularly those located in geographic regions such as Africa or Asia where reliable refrigeration may not be available.

A unique element of the claimed invention is that the method of formulating uses a multilamellar liquid crystal phosphatidylcholine non-polar carrier. The structure of the multilamellar liquid crystal carrier is obtained through the claimed method as specifically described in the Specification, at ¶[0019](Page 7, lines 10-23); and ¶[0018](Page 7, lines 4-9).

Rejection of Claims 1-6, 8, and 11-16 under 35 USC §112  
as Failing to Comply With Written Description Requirement

The Examiner has rejected Claims 1-6, 8, and 11-16 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Specifically, the Examiner has objected to the claim limitation “non-liposome multilamellar crystal non-polar phosphatidylcholine” and stated that the topical delivery compositions are non-polar in [0010] but not that the phosphatidylcholine is non-polar and that the topical drug delivery compositions may be in liquid crystal phase but not crystal phase. (Final Office Action at 2).

Claim 1 recites: “a non-liposomal multilamellar liquid crystal phosphatidylcholine **non-polar carrier** entrapping said drug, wherein said carrier stabilizes said drug at room temperature.” The claim language does not state “non-polar **phosphatidylcholine**” but instead recites a “non-polar **carrier**.” The amended claim

language is consistent with the indication of the Examiner in the Final Office Action at p. 2 that “topical delivery compositions are non-polar” and that “the topical drug delivery compositions may be in liquid crystal phase.”

Specific support for the claim language is found in the application at ¶[0009] (Page 3, line 7), which specifies that the “stabilized insulin compositions are...nonpolar.” The application further specifies at ¶[0013] (Page 4) that:

it is believed that the PPC-enriched phosphatidylcholine forms a bilayer enveloping insulin to create the stabilized insulin compositions, contributing to the stability of the insulin molecules and enhancing penetration. Further, the stabilized insulin compositions. . . may be in liquid crystal phase, with the PPC-enriched phosphatidylcholine loosely arranged in multilamellar fashion, with the polypeptide or macromolecule being bonded and entrapped within the lipid bilayers formed therein. This forms a loosely arranged, yet stable, PPC-enriched phosphatidylcholine-insulin complex that further increases penetration and delivery of the polypeptide or macromolecule to the dermal vasculature.

Clearly the specification as filed defines subject matter which includes a ***multilamellar liquid crystal*** phosphatidylcholine. The ***multilamellar liquid crystal*** has ***bilayers*** entrapping the compound to be administered. Paragraph [0009] further specifies that the topical delivery compositions are ***nonpolar***. Although the term “non-liposomal” is not specifically referred to in the specification, a person of average skill in the art would know that a ***multilamellar liquid crystal*** is not a liposome. It is supported by the disclosure of the specification that the phosphatidylcholine is a multilamellar liquid crystal.

It is respectfully submitted that a person of ordinary skill in the art would consider

the subject matter of the claims to be reasonably conveyed by the specification, and the rejection of claims 1-6, 8, and 11-16 under 35 U.S.C. §112, first paragraph should be reversed.

Rejection of Claims 1-6, 8, and 11-16 under 35 USC §112 as Indefinite

The Examiner has rejected claims independent claim 1 under 35 U.S.C. §112, second paragraph as being indefinite on the grounds that “non-polar carrier” is indefinite. (Final Office Action at 3). The Examiner states that it is unclear how the carrier can be non-polar when it contains polar phosphatidylcholine. Claims 2-6, 8, and 11-16 are rejected on the grounds that they are dependent on indefinite base claims.

(*Id.*)

Claim 1 is not indefinite. Polar molecules form a variety of structures in aqueous media by self-association, depending on water content and temperature. The addition of small amounts of water to many polar lipids results in the initial formation of a reverse micellar solution. As the water content and/or temperature increase, different mesophases such as lamellar, reversed hexagonal, bi-continuous cubic, and isotropic sponge phase are formed. In particular cubic liquid crystals are transparent, isotropic viscous phases and are physically stable in excess water. See e.g. Esposito, *Lipid-Based Supramolecular Systems for Topical Application: A Preformulatory Study*, AAPS PharmSci 2003; 5 (4) Article 30 submitted in the Evidence Appendix. Such crystal mesophases are the “non polar carriers” as claimed in the invention. There are numerous examples polar molecules forming larger nonpolar superstructures (i. e. non-

polar carriers). Examples of such from common experience are soaps, detergents, inks, fabric softeners and ski wax.

In this case, the term “non-polar” describes a multilamellar liquid crystal structure which is stable and not prone to form polar structures such as liposomes, emulsomes, micelles or reverse micelles. It is respectfully submitted that a person of ordinary skill in the art will consider the term “non-polar carrier” to be definite, and the rejection under 35 USC §112, second paragraph should be reversed.

Rejection of claims 1-6, 8, and 11-16 under 35 USC §103(a)

Claims 1-6, 8, and 11-16 are rejected under 35 USC §103(a) as being unpatentable over Amselen et al (US 5662932) or Lynch (US 2002/0153509) in view of Hansen (US 4614730) and Patel (US6294192), and with respect to claims 2-6, 8, 15 and 16, Chaiyawat (U.S. 6538061) and Brieva (U.S. 5985298). (Final Office Action at 4-13).

The Examiner states that Amselen discloses a lipid particle having core which is in a liquid crystalline phase that can encapsulate medicaments and that rigid bilayer envelopes are expected. (Final Office Action at 5).

Applicant disagrees with the Examiner’s characterization of Amselen. Amselen specifically discloses and is directed at “emulsomes”, which are liposome-like structures which are fundamentally different from the loosely arranged multilamellar liquid crystal structure claimed in this application. According to Amselen: “[e]mulsomes of this invention are distinct from standard oil-in-water emulsions. Due to the high phospholipid

content of the current invention, a **monolayer** of phospholipid surrounds the lipid core at the aqueous interface thereby stabilizing the emulsion.” (Amselen, Col. 13, lines 35-45; also Col. 6, lines 50-57.) The phospholipid monolayer is a **polar** structure around the lipid core. (Amselen, Col. 6, line 53.)

A key component of the emulsomes taught by Amselem is the presence of an entirely hydrophobic neutral lipid core. The present invention contains no neutral lipid core. In contrast to the 0.5:1 to 1.5:1 phospholipid/core lipid weight ratio as described by Amselem, the phosphatidylcholine/lipid weight ratio of the present invention is 1:0 *since no core lipid is present*. Furthermore, the lipid core in Amselen is **not** a phospholipid, nor is it phosphatidylcholine. It is a triglyceride. (Amselen, Col. 4, line 23-Col. 5, line 60). Amselen uses phospholipids as the surrounding envelopes of emulsomes phosphatidylcholine “ (Amselen, Col. 6, lines 65-67).

Amselen certainly does not disclose or suggest a method of formulating a stable insulin composition by preparing a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier for topical administration; and mixing an insulin solution into the carrier to entrap insulin within the carrier and to stabilize it at room temperature.

Lynch et al teach of a “cubic liquid crystalline phase precursor comprising (A) an ambiphile capable of forming a cubic liquid crystalline phase, (B) an optional solvent and (C) an additive selected from the group consisting of an anchor, a tether and combinations thereof such that  $1.0=A+B+C$  and  $1>A>0$ ,  $1>B>0$  and  $1>C>0$ . (i.e each of

A, B and C must be present in some quantity). The “tether” C is identified as having a charged end and a lipid tail in [0054] to [0059].

Lynch notes that the formulation of liquid crystal compositions is unpredictable, stating that “Cubic liquid crystalline phase materials are limited in use due to restriction of their natural, or unmodified, properties. For example, the natural properties of cubic phases limit the ability to solubilize active ingredients. In fact, broad classes of actives do not effectively load (or subsequently release) because the cubic phase lacks specific interaction with the loaded active. If the active is modified to effectively load in the cubic phase, it may lose its effectiveness.” *Id* at ¶[0010].

Lynch emphasizes the importance of the anchor and/or tether component “C” as an integral part of the composition. Specific examples of such components are specified at ¶¶[0054]-[0062].

The formulation method of the present invention does not require an anchor and/or tether component “C” as specified in Lynch. As Lynch points out, the formulation of liquid crystalline phase materials is unpredictable, and it would not be obvious to omit a key component of Lynch to arrive at the claimed invention.

Lynch discloses cubic liquid crystals, and does not disclose lamellar liquid crystals. Liquid crystals can exist in many different phases, which include Discontinuous cubic phase (micellar cubic phase); Hexagonal phase (hexagonal columnar phase) (middle phase); Lamellar phase; Bicontinuous cubic phase; Reverse hexagonal columnar phase ; Inverse cubic phase (Inverse micellar phase). Each phase has distinct properties and the formulation of a cubic phase composition for small

molecule pharmaceutical applications does not disclose or suggest a multilamellar liquid crystal phase used with an insulin solution.

Hansen (US 4,614,730) discloses insulin solution containing water, dissolved insulin, one or more of the phospholipids for parental administration. Hansen does not disclose, nor enable a method for formulating a topical insulin composition using a ***non-liposomal*** multilamellar liquid crystal phosphatidylcholine non-polar carrier.

Patel et al. teach a pharmaceutical composition to topical drug delivery of therapeutic agents comprised of at least one hydrophobic and one hydrophilic surfactant. Patel, in teaching on the use of two components, one hydrophilic and one hydrophobic, teaches away from the use of ambiphils such as those described in the present invention. Patel does not mention the combination of polyethylene glycols (PEGS) with PPC-enriched phosphatidylcholines to produce the multilamellar structures described within the instant invention. The Examiner cites Patel et al. for disclosing the use of polyethylene glycols (PEGS) having a molecular weight of 200 to 6000 as a solubilizing agent in a formulation for topical/transdermal delivery. Patel et al. discloses the formulation of hydrophobic therapeutic compounds with a hydrophilic surfactant and a hydrophobic surfactant to solubilize the hydrophobic therapeutic compounds; including use of polyethylene glycol ("PEG") compounds. Patel et al. teach a pharmaceutical composition principally for oral administration of *hydrophobic* therapeutic agents, having poor solubility in aqueous solution, comprised of at least one hydrophobic and one hydrophilic surfactant. Insulin is not an agent within the scope of Patel. Although insulin has a hydrophobic core, the surface residues are polar making it possible to exist

in solution in the blood. Patel does not mention the combination of polyethylene glycols (PEGs) with phosphatidylcholines to produce the multilamellar structures as claimed in the present application. Accordingly, in addition to the reasons stated above with regard to Amselen, the proposed combination of Amselen and Patel would not make claims 1-6, 8, and 11-16 obvious to a person of ordinary skill in the art, as that person would have no reason to combine the two references.

Chaiyawat et al. teach the use of silicone fluids such as dimethicone as carriers of drugs for topical administration. Chaiyawat does not describe these silicone fluids as lubricants but as the carriers (i.e. solvents) for the drugs themselves. As such there would be no motivation for one of average skill in the art to combine the teachings of Chaiyawat with those of Amselem to arrive at the present invention. Chaiyawat does not mention the use of phosphatidylcholines to produce the multilamellar structures described within the instant invention.

Brieva et al. discloses trimethylated silica/ polysiloxane polymer mascara compositions. Brieva discloses cosmetic compositions comprised of non-volatile silicones, such as Dow 190, for improved long lasting adherence to the skin of cosmetics. The present invention is not directed toward cosmetics. Brieva does not mention the use of phosphatidylcholines to produce the multilamellar structures described within the instant invention.

The present invention provides for a method of formulating an insulin composition within a phosphatidylcholine carrier, wherein said insulin is stabilized at

room temperature. Neither the disclosed invention nor its benefits are disclosed or suggested by the combination of references.

Claims 1-6, 8, and 11-16 are patentable over Amselem et al. or Lynch in view of Hansen and Patel, and claims Claims 2-6, 8, and 15-16 are patentable over the four cited references plus Chaiyawat and Brieva. The rejection under 35 U.S.C. §103 should be reversed.

Furthermore, none of the cited references suggest or disclose the combination of phosphatidylcholine and polyglycols of two different molecular weights (200 and 400), and for this additional reason, claims 2 and 3-6, and 8 are patentable over the cited art. Since both Amselem et al. and Lynch disclose particular working formulations, one of average skill in the art would have no motivation to modify this carrier by addition of PEG 200 and PEG 400 with the expectation of arriving at a multilamellar liquid crystal.

In the same way, the process steps of claims 5 and 16 are not disclosed or suggested by the cited art. These claims call for the phosphatidylcholine solution is warmed to 40°C and milling the warmed solution; and that siloxylated polyether and polydimethylsiloxane are combined to form a fluid which is added to the warmed solution; and that methyl paraben is added to the solution and milled until it dissolves; and that water warmed to 40°C is added slowly to said solution; then cooled to room temperature while sweeping it. Neither these method steps, nor any analogous methods, are disclosed or suggested by any of the cited references.

In addition, with respect to claims 5-6, and 16, one would have no motivation nor reason to use lubricious silicone fluids and/or siloxylated polyethers such as DOW 190

and/or preservatives. There is no motivation provided by the references to combine them into the claimed invention.

The specific and detailed claims 4-8 and 16 define the specific method which results in the unique multilamellar liquid crystal. These specific steps provide the new and unexpected result of creating a stable insulin solution which is the key product of the method of the invention.

The present invention provides for a method of formulating an insulin composition within a phosphatidylcholine carrier, wherein said insulin is stabilized at room temperature. Neither the disclosed invention nor its benefits are disclosed or suggested by the combination of references, and a person of ordinary skill in the art would have no reason to combine the references to arrive at the claimed invention. Further, even if the references were combined as suggested by the Examiner, they still would not arrive at the claimed invention. The combination of Amselen, Patel, Chaipayat, Brieva and Hansen would not provide the claimed invention. Accordingly, claims 1-6, 8, and 11-16 are patentable over Amselen in view of Patel, Chaipayat, Brieva and Hansen, and the rejection of these claims under 25 U.S.C. §103 should be reversed.

There is no disclosure in the cited references of a providing a method of formulating a room temperature stabilized insulin composition as described in the present claims and specification. Neither the disclosed invention nor its benefits are disclosed or suggested by the cited references. The presently claimed invention is inventive over the cited prior art.

Conclusion

The claims of the application meet all requirements of 35 U.S.C. §112.

The cited references do not disclose or suggest the claimed method for formulating a non-liposomal multilamellar liquid crystalline phosphatidylcholine non-polar carrier. It is submitted that the claimed invention would not have been obvious to a person of ordinary skill in the art at the time of the invention thereof. Accordingly, for all of the foregoing reasons, the rejection of the claims should be reversed, and it is respectfully requested that the Examiner be directed to issue a Notice of Allowance of these claims.

Respectfully submitted,

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**(viii) Claims appendix**

1. A method of formulating a topical insulin composition comprising:  
preparing a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier for topical administration; and mixing an insulin solution into said carrier to entrap said insulin within said carrier, wherein said insulin is stabilized at room temperature.
2. The method of claim 1, wherein preparing said carrier comprises:  
combining a polyglycol having a molecular weight of 200 and polyglycol having a molecular weight of 400 to form a polyglycol mixture;  
shaving said phosphatidylcholine into said polyglycol mixture to form a phosphatidylcholine solution; and  
mixing said phosphatidylcholine solution until said phosphatidylcholine solution is clear.
3. The method of claim 2, wherein said phosphatidylcholine component is polyenylphosphatidylcholine-enriched phosphatidylcholine.
4. The method of claim 2, wherein said phosphatidylcholine solution comprises 45% w/w phosphatidylcholine, 50% w/w polyglycol having a molecular weight of 200, and 5% w/w polyglycol having a molecular weight of 400.
5. The method of claim 2, wherein preparing said carrier further comprises  
warming said phosphatidylcholine solution to 40°C and milling said warmed solution;  
combining siloxylated polyether and polydimethylsiloxane to form a fluid;  
adding said fluid to said warmed solution carrier and milling until said solution is clear;

adding methyl paraben to said solution and milling until said methyl paraben dissolves in said solution;

warming water to 40°C and adding said warmed water slowly to said solution; and

ceasing milling of said solution and sweeping said solution to cool to room temperature.

6. The method of claim 5, wherein said carrier comprises 53.25% w/w phosphatidylcholine solution, 1.00% w/w siloxylated polyether, 1.00% w/w polydimethylsiloxane, 0.75% w/w methyl paraben, and 44.00% w/w water.

7. Cancelled

8. The method of claim 6, wherein said wherein said siloxylated polyether is dimethyl, methyl(propylpolyethylene oxide propylene oxide, acetate) siloxane.

9. Cancelled

10. Cancelled

11. The method of claim 1, wherein said insulin solution is human recombinant insulin prepared in 0.01 N HCl.

12. The method of claim 11, wherein said insulin is prepared in 0.01 N HCl at 50 mg/ml.

13. The method of claim 1, said insulin solution is mixed into said carrier at room temperature for at least one hour.

14. The method of claim 1, said insulin solution is mixed into said carrier to obtain said insulin composition having a concentration of 20 mg/ml.

15 The method of claim 1, wherein preparing said carrier comprises:  
providing a polyglycol;  
shaving phosphatidylcholine into said polyglycol to form a phosphatidylcholine solution; and  
mixing said phosphatidylcholine solution until said phosphatidylcholine solution is clear.

16. The method of claim 15, wherein preparing said carrier further comprises  
warming said phosphatidylcholine solution to 40°C and milling said warmed solution;  
combining siloxylated polyether and polydimethylsiloxane to form a fluid;  
adding said fluid to said warmed solution carrier and milling until said solution is clear;  
adding methyl paraben to said solution and milling until said methyl paraben dissolves in said solution;  
warming water to 40°C and adding said warmed water slowly to said solution; and  
ceasing milling of said solution and sweeping said solution to cool to room temperature.

**(ix) Evidence appendix**

Esposito, *Lipid-Based Supramolecular Systems for Topical Application: A Preformulatory Study*, AAPS PharmSci 2003; 5 (4) Article 30.

**(x) Related proceedings appendix**

***None***